IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	**Confirmation No. 5291**
Mie TAKAHASHI et al.	:	Attorney Docket No. 2001_1464A
Serial No. 09/937,730	:	Group Art Unit 1641
Filed January 8, 2002	:	Examiner Gary W. Counts
CHROMATOGRAPHY MEDIUM AND ITS MANUFACTURING METHOD	:	**Mail Stop: Amendment**

RESPONSE

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEES FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Responsive to the Office Action of December 10, 2007, Applicants submit the following remarks in support of the patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims. Further and favorable reconsideration is respectfully requested in view of these remarks.

Rejection Under 35 U.S.C. § 103(a)

The rejection of claims 5, 12, 27, 31, 41, 45, 53 and 60 under 35 U.S.C. § 103(a) as being unpatentable over Chu (U.S. 6,284,194) in view of Nanbu et al. (U.S. 6,130,055) or Uenoyama et al. (U.S. 5,856,117), as well as the rejection of claim 49 under 35 U.S.C. § 103(a) as being unpatentable over Chu in view of Nanbu et al. or Uenoyama et al. and further in view of Iwata et al. (U.S. 5,912,139), are respectfully traversed.

Discussion of Applied References

Applicants agree with the Examiner's opinion that Chu discloses an analytical device and method of making the device. Chu teaches that the device comprises a porous reaction

membrane and at least one receptor immobilized in a limited region (reaction layer and reactive components). Chu also teaches applying a surfactant (surface active agent) to the reaction membrane and allowing it to dry, wherein the drying can be performed by air drying at room temperature, or by warm air with good ventilation. Chu further teaches that the surfactant may be a surfactant such as polyoxyethylene, polyoxyethylene sorbitan monolaurate, or polyoxyethylene sorbitan monooleate. Lastly, Chu teaches that all or most of the surface is exposed to the surfactant.

Applicants also agree with the Examiner's opinion that Nanbu et al. disclose surfactants (surface active agents). Specifically, Nanbu et al. disclose that the surfactant may be polyoxyethylene, sorbitan monolaurate, polyoxyethylene sorbitan monooleate, or sucrose monolaurate. Nanbu et al. also teach that the use of a surfactant improves the assay sensitivity.

Further, Applicants agree with the Examiner's opinion that Uenoyama et al. disclose surfactants (surface active agents). Uenoyama et al. disclose that the surfactant may be polyoxyethylene, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, n-octyl-B-D-thioglucoside, or sucrose monolaurate. Uenoyama et al. also teach that the use of a surfactant improves the assay sensitivity.

As for the drying step, the Examiner indicates that Chu teaches that drying can be performed by warm air in good ventilation. Applicants agree that drying is generally known as a chemical experiment method. However, polyoxyethylene sorbitan monolaurate is a slightly yellow liquid surface active agent at normal temperature and normal pressure. Also, polyoxyethylene sorbitan monooleate is a slightly yellow liquid surface active agent at normal temperature and normal pressure. From a physical standpoint, drying the liquid surface active agent at normal temperature and normal pressure means: 1) evaporating the surface active agent itself, or 2) evaporating the surrounding water without drying the surface active agent. Following option 1), evaporating the surface active agent itself, does not make sense because the surface active agent does not remain on a test specimen. Following option 2), evaporating surrounding water without drying the surface active agent as in the latter case, the surface active agent remains on the test specimen in liquid form because the surface active agent is in liquid

state at normal temperature and normal pressure.

With the surface active agent which leaves a liquid material on a test specimen after having a drying process, the test specimen using such surface active agent would cause a decline of long-term preservation stability. Even though a high sensitivity state could eventually be obtained at an early phase after manufacturing, the sensitivity will decline during the period until the user actually uses the product, after marketing. Accordingly, the user would obtain incorrectly measured results based on a test specimen with decreased sensitivity. At that time, in a field of bioassay, especially for a test specimen which is used in a clinical field, ensuring long-term preservation stability and increasing preservation circumstance freedom are major issues.

Discussion of Patent Documents to Show Importance of Preservation Environment and Stability

The following discussion relates to Japanese patent application documents which reinforce that preservation environment and long term preservation stability are very important issues in the field of Applicants' invention.

For Example, for a device and a method for obtaining an analytical target ratio which is clinically important, Kuo et al. teach a correcting curve for an immunochromatography test specimen format, which is preserved in a reflectance device to calculate a density of analytical target. (Patent document 1, Japanese Published Patent Application No. Hei11-083856, 1997.7.25, Kuo et al.). This indicates that it is possible to calculate a density of an analytical target according to an early phase regression formula even though time has elapsed prior to the user actually using it after shipment, by determining a regression expression based on when the test specimen is manufactured and shipped. That is, when a sensitivity of the test specimen has degraded with time, an incorrect measurement result would be given, which is a very important problem.

Also, Doi teaches a method involving one or more stabilizers selected from a group of saccharose, trehalose, ß-cyclodextrin, threonine, aspartic acid, tryptophan, glutamic acid, asparagine, histidine, glutamic acid-arginine, leucyl glycine, glycyl thyrosin, phenyl alanine, and

calcium chloride in a solution when lyophilizating a liquid containing a sensitized metal colloid, as a production method that stabilizes a lyophilization product containing a sensitized metal colloid, and a lyophilization product containing a sensitized metal colloid which can be stored for long period. In Doi, it is described that it is possible to improve the stability of a reagent, mainly a sensitized metal colloid in a lyophilized state in a field of clinical assay, so the sensitized metal colloid reagent becomes available for a long preservation term. Therefore, elongation of duration of use of the reagent and improvement of measurement accuracy can be achieved in a field of clinical assay using a sensitized metal colloid reagent. (Patent document 2, Japanese Published Patent Application No. Hei11-125635, 1997.10.21, Doi).

Also, in a field of an apparatus which tests biologically interested analytes, there is a need to both facilitate the ease of closure and to ensure secure closure during shelf life up to the point of use, as well as after closure, during the performance of the assay, to facilitate disposal of the device. Shields et al. teach providing secure closure, facilitating the ease of closure, and ensuring secure closure during shelf life up to the point of use, and during use, as an improved housing for verification apparatus of bevel closure. (Patent document 3, Japanese Published Patent Application No. Hei11-2816456, 1997.11.17, Sheilds et al.)

Kawasaki et al. teach that for a dry analysis method and dry analysis element which can easily and sensitively analyze a specimen by detecting aggregation of the test substance (e.g. an antigen) and a label-specific bonding substance which is obtained by bonding a specific bonding substance (e.g. an antibody) to a labeled carrier (e.g. a metal colloid), in a field of medical, diagnosing the condition of diseases, and judging the medical treatment, the immunoassay method of that time is useful in that it does not require B/F separation. However, in this method, the latex reagent is poor in storage stability, since it is in the liquid state. Also, in the colloidal gold agglutination method, the colloidal gold solution is inferior in storage stability as a reagent. Therefore, it is necessary to mix lyophilized colloidal gold-labeled reagent with a dedicated solution upon measurement, thus making the operation cumbersome. Also, this method is disadvantageous in that it is not suitable for a measurement of small amounts of a sample.

On the other hand, there is the dry analysis method, which is superior in storage stability

and convenient operation. Under such a circumstance, as a result of searching for a material capable of causing agglutination in a layer medium of a dry analysis element, it succeeded in causing an agglutination behavior of a colloidal metal in an analysis element quantitatively at good sensitivity by using some kind of medium, while ensuring a storage stability of the reagent which is a characteristic of a dry analysis element. (Patent document 4, Japanese Published Patent Application No. 2001-4629, 1999.6.18, Kawasaki et al. The same is taught in patent document 6, Japanese Published Patent Application No. 2001-21564, 1997.7.12, Nakamura et al.)

Also, Tanaka et al. disclose that in a test piece and a developing composition for enzyme immunochromatography, enzymes such as peroxidase or alkaline phosphatase are used widely as a label combining to a labeled antibody, and measurement of a test material is performed by using color reactions of these enzymes with its substances. However, there is a problem with a stability of enzyme-substance in a developing liquid, and it is indicated that chromogenic sensitivity decreases during a long-term preservation. For such issues, it becomes apparent that the preservation stability of these reagent improves by using a developing liquid not including 3,3',5,5'- tetramethy benzine (TMB) and by applying the TMB directly to a membrane of a test strip. (Patent document 5, Japanese Published Patent Application No. 2001-13144, 1999.6.29, Tanaka et al.). In this document, it is further disclosed that it is desirable to block an absorbable base forming a fixed part with a surface active agent such as polyoxyethylene (20) sorbitan monolaurate (Tween™20), polyoxyethylene (10) sorbitan monooleate (Tween™80), polyoxyethylene (10) octylphenyl ether (Triton™X-100), sodium dodecylbenzenesulfonate, some of which are the same as in Chu, or a protein such as bovine serum albumin, skim milk, casein, or a water-soluble polymer such as polyethyleneglycol, polyvinyl alcohol, or polyvinylpyrrolidone, to prevent nonspecific adsorption of test material. The same is taught in patent documents 8: Japanese Published Patent Application No. 2002-31639, 2000.7.18, Okada et al., 9: Japanese Published Patent Application No. 2002-40026, 2000.7.19, Fujioka et al., and 10: Japanese Published Patent Application No. 2002-122598, Tanaka et al. Especially, in patent document 8, it is taught that from a viewpoint of the preservation stability of a fixed first specific

bonding material, it is desirable to be treated with a liquid containing a blocking agent, surface active agent, and a sugar. As a blocking agent, bovine serum albumin, casein, skim milk, or gelatin may be cited. As a surface active agent, polyoxyethylene (10) octylphenyl ether, polyoxyethylene sorbitan monolaurate, polyoxyethylene alkylallyl ether phosphate, polyoxyethylene alkyl ether phosphate, or polyoxyethylene alkyl phenyl ether may be cited.

Also, Koyama et al. teach providing an immunoanalysis device which can maintain a stability even under long term preservation and/or high temperature preservation and a method for improving a stability of an immunoanalysis device. In an immunoanalysis device using a chromatography strip and a production method thereto in a conventional method that immobilizes antigen or antibody by adsorption into a chromatography carrier, the antigen or antibody binding ratio to the solid-phased chromatography carrier temporarily changes under conditions where a chromatography carrier fixed to antigen or antibody is preserved for a long time and/or at thirty degrees or more (for example at a high temperature of thirty to forty degrees). The change of binding ratio during this preservation period causes a change of chromogenic degree on a detection region, thereby it cannot keep the stability of immunochromatography specimen and a constant result cannot be obtained. It is found that by forming a biotinylated antigen or biotinylated antibody by having a biotin covalently bound to antigen or antibody which is likely to be immobilized to the chromatography carrier, forming an avidin or derivative of avidin- biotinylation antibody or biotinylation antigen complex by having an avidin or derivative of avidin bounded to biotinylation antibody or biotinylation, and then making the complex absorbed into the chromatography carrier, it is possible to obtain a chromatography strip which is superior in stability and in which solid-phased antigen or solid-phased antibody binding ratio does not change with time. (Patent document 7, Japanese Published Patent Application No. 2001-133457, 1997.11.5, Koyama et al.)

Also, Kadota et al. disclose an immunochromatographic detector detecting the test material existing in the lymph node by a marker appearing in the detecting section, which contains a reagent labeled with a marker which can move in a porous substance and a test material-specific reagent which is immobilized to the detecting section of the porous substance,

wherein a serum albumin and a straight-chain water-soluble polymer are arranged with the labeled reagent. (Patent document 11, Japanese Published Patent Application 2002-148266, 2000.11.10, Kadota et al.) In Kadota et al., it is taught that from a viewpoint of preservation stability of a labeled reagent, the amount of straight-chain water-soluble polymer is preferably 0.1 w/t part or more per 1 w/t part of serum albumin, and from a viewpoint of a mobility, specificity, and reactivity, the amount of straight-chain water-soluble polymer is preferably 10 w/t parts or less per 1 w/t part of serum albumin.

Lastly, Matsuura et al. teach the importance of preservation circumstance, e.g., preserving in silica gel desiccator after eliminating blocking solution, even during manufacturing, in providing a rapid and simple immunochromatography process having a sensitivity higher than that of conventional known immunochromatography. (Patent document 12, Japanese Published Patent Application No. 2002-202307, 2000.12.27, Matsuura et al.)

The above documents are discussed in detail to reinforce that preservation environment and long preservation stability were very important technical issues at the time of the presently claimed invention. Also, as Applicants indicated in the present specification, the surface active agents used by Chu are the ones which have been found in the above mentioned reference documents and which are known in the general art.

Arguments Regarding Examiner's Position Regarding Simple Substitution

Despite the fact that the preservation stability is such an important issue at the time of the presently claimed invention, there are no teachings nor suggestions regarding preservation stability in the teachings of Chu, Nanbu et al., and Uenoyama et al. The Examiner takes the general position that the surface active agents of the present invention and the surface active agents disclosed in Chu are equivalent, and thus would be substituted for one another with a reasonable expectation of success. However, assuming *arguendo* that the Examiner's position *regarding equivalency* is accurate, this can only be true with respect to the field of Nanbu et al. and Uenoyama et al., i.e. improvement of the measurement sensitivity of urinary trypsin inhibitor by improving the dissolubility of a hardly-soluble substance and thereby increasing the substrate

addition amount, in a condition that proteinase, low-water solubility substance, organic solvent, or plastic cell are used as elements. There is no teaching or suggestion that the surfactants of Chu and the surfactants of Applicants' presently claimed invention are equivalent in the field of Applicants' presently claimed invention. This is important in traversing the Examiner's assertion regarding a reasonable expectation of success.

MPEP 2143 discusses the Examiner's purported rationale, and the requirements for properly asserting this basis for a rejection based on obviousness. Specifically, to reject a claim based on "simple substitution of one known element for another to obtain predictable results", the Examiner must resolve the *Graham* factual inquiries, and then articulate the following: (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components; (2) a finding that the substituted components and their functions were known in the art; (3) a finding that one of ordinary skill in the art could have substituted one known element for another, **and the results of the substitution would have been predictable**; and (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. The rationale to support a conclusion that the claim would have been obvious is that the substitution of one known element for another yields predictable results to one of ordinary skill in the art. The MPEP further states that **if *any* of these findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art.**

In this case, the result of substituting a surfactant of Nanbu et al. or Uenoyama et al. for the surfactant of Chu **would not be predictable**. Specifically, for the reasons articulated in detail in the Response Filed Concurrently with RCE, Applicants' presently claimed invention, particularly the use of a surfactant which has sugar in a hydrophilic part which is able to become solid when dried, results in many advantageous properties, which would not have been predicted based on the teachings of the prior art. The premise of "merely substituting" one known element for another, is that the elements should behave in a similar manner. However, Applicants have

repeatedly explained that the use of the particularly recited surfactant results in advantageous effects. **The Examiner has provided no support for his assertion that the results of this substitution would be predictable**. Accordingly, based on MPEP 2143, the Examiner cannot rely on the "simple substitution" rationale for maintaining that Applicants' presently claimed invention is obvious.

The Examiner is respectfully requested to review the arguments set forth in the Response Filed Concurrently With RCE, in view of Applicants' additional comments, set forth above.

The presently claimed invention aims to provide a chromatography specimen and its manufacturing method which minimizes the quantity of a marker reagent remaining in the background, enhances the reactivity by improvement in the permeability of a liquid simple and provides a more uniform spread of the liquid sample, and enhances the preservation stability of the chromatography specimen for an issue that a quality maintenance period of the specimen is shortened or a storage condition of the specimen is restricted. By adopting the surface active agent having sugar in a hydrophilic part and having such a property that it can be solidified when dried, as recited in Applicants' pending claims, the devitalization of a reactive component immobilized on the reactive layer can be minimized because the reactive layer is in a completely dried condition until the liquid sample is applied thereto and permeates the reactive layer, thereby realizing the enhanced preservation stability, the extended quality maintenance period, and the expanded storage condition of the chromatography specimen. Therefore, it is possible not only to realize an enhanced sensitivity and enhanced performance chromatography measuring but also to realize the enhanced preservation stability, the extended quality maintenance period, and the expanded storage condition of the chromatography specimen.

For the above discussed reasons, the subject matter of Applicants' claims is clearly patentable over the cited combinations of references. The Examiner is respectfully requested to withdrawn the rejections.